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Original Article

Paediatrics Section

Tolerance of ALL Induction Therapy in Children with Limited Resources: A Retrospective Study from a Teaching Hospital

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ABSTRACT

Introduction: Acute Lymphoblastic Leukaemia (ALL) is the most common malignancy in children. Due to the better understanding of biology, intensive multi-agent chemotherapy and improved supportive care, ALL is curable in majority of children. Induction phase is the most intense and critical phase of therapy.

Aim: To examine the feasibility of high-intensity induction and its tolerance in a resource-limited setting in children with acute lymphoblastic leukaemia.

Materials and Methods: This retrospective analysis was done on children admitted for ALL treatment. Data was collected for January 2016 to July 2018, regarding baseline characteristics, tolerance to induction therapy, morbidity, mortality, deviations from protocol, and induction outcomes among children with ALL treated at a tertiary care teaching hospital (Cancer Research Institute, Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand, India). Confirmed cases of ALL with age upto 18 years, who took more than a week of planned induction were included in the study. Data was analysed using Chi-square and Fisher's-exact test.

Results: Four-drug induction was feasible and given to 76 patients during the study period. Mean age of the group was 9.3 years. Male: female ratio was 1.3:1. Remission was achieved in 63 (82.8%) patients. Four deaths occurred, and were attributed to infection. Hyperglycaemia (4), CNS events (2), peripherally inserted central line related thrombosis (2) and pulmonary tuberculosis (1) were noted. Febrile neutropenia was noted in 65 cases and seven cases required ICU care; two of them succumbed in the ICU. Baseline blood parameters, subtype of disease, protocol of treatment and age did not affect the induction outcome statistically.

Conclusion: Intensive induction chemotherapy has varying complications and can be employed even in resource-limited settings with acceptable results.

Keywords: Acute lymphoblastic leukaemia, Induction chemotherapy, Leukaemia, Sepsis, Supportive care

INTRODUCTION

Paediatric ALL has witnessed a dramatic success with multi-agent therapy over the last four decades. Children oncology group experiences showed a dismal cure rate less than 10% in 1960's, which improved to more than 80% in 1990's and more than 90% in 2001-2005 data [1]. Improvement in survival is to the extent that focus has been partly shifted to decreasing the dose thus minimising the long-term complications of treatment. Better risk stratification and tailoring treatment based on risk, response and minimal residual disease has led to more than 80% cure rate among paediatric ALL cases [2,3]. While data from developing countries is scarce, public health sector in India has failed to display such results and cure rates are remarkably low varying from 25-40% [4-6].

Induction period is the most critical period for any ALL children. Children often present with deranged haematological parameters, infections and poor nutritional state. Multi-agent chemotherapy protocols are myelo-suppressive and vulnerability of children to organ damage, sepsis and death is high [6]. A good supportive system is required for induction phase of chemotherapy. Indian pooled data noted about 10% of death in induction phase of chemotherapy [7]. Infection-related deaths have been noted to be one of the main reasons of poor outcome in childhood leukaemia. Resource constrains in form of poor staff training and staff to patient ratio has been noted in low/middle income country. Cross-sectional data survey from 54 countries showed direct relation of quality of childhood cancer nursing with country income and health expenditure [8]. Availability of healthcare workers in Africa is far less than recommended by developed countries [9]. Data from India also showed poor nurse to patient ratio in multi-hospital survey [10]. Availability and use of Pegylated L-Asparaginase, which has shown to improve the result of childhood ALL, has been noted to be poor in India [11]. Non affordability to newer treatment plans incorporating minimal residual disease assessment also contribute to poor outcome. In a survey done by International Society of Paediatric Oncology in 2014, nursing care in paediatric oncology wards in low-middle income countries were found sub-optimal and probably the cause of poor outcome [12]. A survey of Government hospitals in Delhi, India also noted sub-optimal ratio of staff to patient in children oncology unit [13].

Cancer research institute is a referral cancer centre in the state of Uttarakhand in India. It is the main referral centre for paediatric malignancies in the region. It caters the middle-income and low-income group population, the majority of who are partly sponsored by various agencies. Authors present the data on childhood ALL induction depicting tolerance, complications and induction outcome. This study will address the feasibility of using intensive multidrug induction chemotherapy in public health sector.

MATERIALS AND METHODS

This was a retrospective observational study conducted at Paediatric Oncology Unit, Cancer Research Institute, Himalayan Institute of Medical Sciences, Dehradun, Uttrakhand, India. Study was conducted in October 2019 to March 2020. Data of children admitted to Paediatric Oncology Unit was collected. Patients enrolled from January 2016 to July 2018 were selected for analysis. Ethical Clearance was taken from research and Ethics Committee (HIMS/RC/2019/04).

Inclusion criteria: All confirmed case of ALL (either on Flow cytometry, or on morphology and PAS block positivity) with age group of less than 18 years in the defined study period and relapsed ALL cases started on salvage chemotherapy, were included in the study.

Exclusion criteria: Patients who had not received induction chemotherapy in this centre were excluded. Patients who died before eighth day of chemotherapy were also excluded from the study.

Procedure

Data (chemotherapy protocol, agents and dose) were collected from digital case records and physical files from medical record section. Any reduction in dose or deviation from schedule of chemotherapy was noted with reason mentioned in records. Day 8 absolute blast counts were noted to check prednisolone response criteria. Central Nervous System (CNS) disease status was noted based on baseline Cerebrospinal Fluid (CSF) cytology, noted clinical features and brain imaging, if done.

Institutional protocol of febrile neutropenia was taken as standard practice and data were collected regarding all febrile episodes in induction. For all practical purpose, fever in initial 3 weeks of induction was taken as febrile neutropenia. Data regarding antibiotic choice, use, duration, and escalation were noted. Cases treated for pulmonary aspergillosis on presumptive basis were noted for Computed Tomography (CT) chest findings and cases with reactivation of tuberculosis was noted in detail regarding basis of starting antitubercular medications.

Postinduction bone marrow report was noted for each case and blasts less than 5% were considered in complete remission. More than 5% blasts were considered induction failure cases. Persistent CNS positivity at this point is also taken as induction failure. Deaths during induction were noted along with cause.

STATISTICAL ANALYSIS

Patient's demographic parameters and baseline characteristics were summarised as descriptive variables. Categorical variables were reported with frequency and percentage while continuous variables were reported as median and range or mean and standard deviation. Cases were grouped into two, based on protocol used and induction mortality and toxicities were compared by using Fisher's-exact test. All cases were further divided into two groups based on outcome of induction. Achieved remission included cases that achieved complete remission and no remission included cases that had induction failure, drop out or death as induction outcome. Both groups were compared using Chi-square test for various affecting variables. The p-value <0.05 was considered as statistically significant. The statistical analysis was done by Statistical Package for the Social Sciences (SPSS) statistics for windows, version 16.0 (SPSS Inc. Chicago 1Il., USA).

RESULTS

Total of 86 children were diagnosed with ALL during this study period. Out of those diagnosed ALL, 10 cases left treatment in less than a week due to various reasons and were thus, excluded from the study. All analyses were done on 76 cases.

Mean age of the group was 9.3 years (5.3). Male: female ratio was 1.3:1. Pre B- ALL was the most common subtype (54%) followed by T- ALL (23%). ALL phenotype could not be ascertained in 23% patients. Those were diagnosed as ALL based on PAS block positivity along with morphology of blasts on bone marrow.

At diagnosis, two patients were detected to have malignant cells in CSF analysis. None of them had focal sign or headache. One case had headache and evaluation showed multiple CNS bleed. He was also treated as CNS positive case. Anaemia was noted among 81.5% children. Total 33% cases had Total Leucocyte Count (TLC) more than 50,000/cmm at presentation, and 10.5% had more than 0.1 million/cmm. Platelet less than 20000/cmm were noted among 81.5% cases [Table/Fig-1]. Serum Lactate Dehydrogenase (LDH) was elevated (>250 IU) in 34 patients (44.7%) and serum uric acid was elevated in three patients (0.4%). Only one case was noted to experience tumourlysis syndrome based on laboratory criteria, and he was managed conservatively.

Parameters	Number (n)	Percentage (%)
B- ALL	41	54
T-ALL	18	23
Biphenotypic	0	0
Not subtyped	17	23
Protocol-BFM ALL based	51	67
Protocol- CCG 1961	25	33
Haemoglobin (Mean±SD)=7.2±3.4 gm/L		
Baseline Haemoglobin <10 gm/L	62	81.5
Total Leucocyte Count (TLC) Mean±SD=24000/cmm (11500)		
TLC >1 Lac/cmm	8	10.5
TLC 50000-100000/cmm	17	22.5
TLC < 50000/cmm	51	67.1
Platelets Mean±SD=12000/cmm (9600)		
Platelets <20,000/cmm	62	81.5
Day 8 absolute blast count (>1000/cm)	3	3.9
Serum LDH (>250 IU)	34	44.7
Serum Uric Acid (>7.5 mg/dL)	3	0.4
Fever	65	86
Culture proven sepsis	4	5.2
Respiratory distress requiring oxygen support	10	13.1
Intensive care unit shifting	7	9.2
Ventilator support	2	2.6
Ionotropes support	5	6.5
Central Nervous System (CNS) events	2	2.6
Thrombosis	2	2.6
Pancreatitis	0	0
Tuberculosis	1	1.3
CNS disease	2	2.6
Death during induction	4	5.2
Remission	63	82.8

[Table/Fig-1]: Baseline characteristics and induction events of enrolled cases (n=76).

Allopurinol and hydration were given to all cases, however, three cases required Rasburicase for high uric acid (>9 mg/dL). Allopurinol was not given to them simultaneously with Rasburicase. Total 16 cases presented with high fever and oral antibiotic (cefixime) was started in them. Five cases required up gradation to injectable antibiotics (Cefeperazone- Salbactum) at onset due to sick condition and sepsis. Cases with fever at presentation, without any obvious infection focus and stable general condition were started on oral antibiotics considering possibility of disease related fever. However, escalation of antibiotics were done to injectable 3rd generation cephalosporin in case of detoriation. None of them showed any culture positivity for baseline fever. Fever episode during induction was noted among 86% of cases however, only four of them showed culture positivity (two for *Klebsiella*, one each for *Staphylococcus aureus* and *Escherichia coli*). Antibiotics were modified based on culture report. Three patients were noted pulmonary aspergillosis and treated with amphotericin B. Two of them were shifted to oral voriconazole after one week. Intensive care unit shifting was required for seven cases and sepsis was the most common cause (among five) followed by seizure and respiratory distress. Ventilation was required for two cases and both of them succumbed to clinical sepsis, although cultures were sterile. Mucositis was the most common side effect noted among 15 cases (more than or equal to grade II as per CTCAE version 4) [14]. Pleural effusion was noticed in one patient and two patients developed hyperglycaemia warranting insulin therapy during induction. Peripherally Inserted Central Catheter (PICC) was placed among 13 cases and four cases, required removal of it during induction, two due to thrombosis and

two due to non resolving fever. One case was diagnosed to have pulmonary tuberculosis during 3rd week of induction. Three drugs antitubercular treatment was started to him.

CNS event in form of seizure was noted among two cases, MRI showed normal finding in both. Steroid induced hyperglycaemia was noted among four cases, all had polyuria and polydipsia. They were managed with insulin. No routine sugar monitoring protocol was in place for asymptomatic induction cases.

Treatment deviations: Nine cases required premature tapering of steroid due to sepsis/aspergillosis. Steroid was restarted among four of them and target of giving minimum of three weeks steroid with tapering was achieved. Remaining five cases received median of 17 days of steroid only. Dose of chemotherapy was reduced (>20%) among six cases, all due to sepsis. Two cases received only two doses of anthracyclins during induction. Maximum dose tempering was done during 3rd week of therapy. Vincristine related neuropathy was noted in one case in form of foot drop. Constipation was noted among 32 cases, however as everyone was on ondensetrone and fluconazole, causation and association with vincristine could not be ascertained. No pancreatitis or thrombosis was noted. L-asparaginase was well-tolerated in all cases. Interruption and delay was noted in following order- daunomycin, steroid and vincristine. Three cases required two additional doses of intrathecal methotrexate for their CNS positivity. Tolerance of chemotherapy had no association with initial haematological parameters.

Outcome of Induction: Out of 76 cases analysed, 82.8% achieved complete remission. Four deaths were noted during induction, all due to sepsis (fever with organ system involvement features). Median timing of death was day 19 of induction. Induction failure was noted among five cases. Four cases left hospital before induction completion despite counselling, three due to financial constrain and one opted out of allopathic treatment. Eight out of 76 cases were relapsed ALL, earlier treated with another protocols {three on UK-ALL, two on Berlin-Frankfurt-Munich (BFM) ALL 95 and two on Multi- Centric Protocol (MCP)-841 protocol}. Out of these relapsed cases, five achieved remission (four on BFM-ALL 95 protocol and one on BFM-REZ protocol). No difference in induction outcome was noted between high TLC, low platelets, chemotherapy protocol, baseline anemia, age with induction outcome [Table/Fig-2]. Biochemical parameters except createnine, serum LDH and uric acid were not evaluated in all cases at baseline. Levels of createnine, LDH and uric acid at baseline did not affect induction outcome. Sepsis, interruption of treatment or baseline characteristics was not associated with induction outcome in term of disease control among survivors.

Parameters (cases completed induction)	Achieved remission	No remission/ death	Chi-square (p-value)
Age			
≤10 years	25	8	0.141
>10 years	38	5	
Protocol			
ALL- Berlin-Frankfurt-Munich 95	45	6	0.132
Children's cancer group	18	7	
Baseline Haemoglobin			
≤10 g%	51	11	1.22
>10 g%	12	2	
Total leukocytes count			
≤1 Lac/cmm	59	10	0.42
>1 Lac/cmm	4	3	
Platelets			
≤20000/cmm	52	11	0.76
>20000/cmm	11	2	
Dose			
Dose interruptions (≤10%)	6	6	1.46
No dose interruption (<10% deviation)	57	7	
Total (n=76)	63	13	

[Table/Fig-2]: Parameters affecting induction outcome.

DISCUSSION

India has approximate 10,000 cases of ALL yearly. Lack of national registry and reporting system makes this figure doubtful for the true prevalence of disease [15]. While about 56% of population is residing in villages and accessibility to healthcare is poor, exact estimation of occurrence including undiagnosed cases are not feasible. Despite all this disparity, focal data published from individual centres has shown improvement in survival [4,16].

Majority of protocols are based on four drug induction with steroid, anthracyclins, vincristine and L-asparaginase along with CNS prophylaxis with intrathecal methotrexate. Results noted by these trials are also comparable. Our centre opted two different protocols, based on consultant preference and experience, BFM ALL 95 and Children's cancer group study 1961 protocol. Both protocols are having same drugs with minor reshuffling of sequences.

Baseline parameters were variable in this study regarding haemogram. High Total Leucocyte Counts (TLC) has been noted to have negative impact on final outcome in studies. Earlier concept of tumour burden was there for affecting outcome, but not considered significant now. Probably increased intensity of induction surpasses the ill effects of tumour burden. Steroid response is more accurately associated with outcome and has been included in risk stratification in BFM and other major trials [17-19]. Initial haemogram variables were not different in remission and induction failure cohorts. This study was having limited number of cases to conclude impact of haemogram variables on induction outcome.

Infections and sepsis remains major cause of death during induction treatment. Gram negative septicaemia has been noted in majority of deaths in various studies from India and abroad. Klebsiella and Pseudomonas has been noted as most common pathogens [20,21]. Decreased immunity due to disease and on-going ablative induction chemotherapy makes the patient a vulnerable prey of microbes. Intestine microbes remain the main source of infection and with gut mucositis, risk increases significantly [22]. This study noted four febrile neutropenic cases having growth in blood culture, out of which three were gram-negative organism. Spore of aspergillus is common in dust and environment where dust exposure is common, risk of aspergillus remains high. Central Research Institute (CRI) facility is located at outskirt area and patient coming to this center often travel variable geographical terrains. Aspergillosis risk further increases with on-going constructions in state for government proposed highways. This study noted three cases of pulmonary aspergillosis during induction. As aspergillosis was detected only by CT chest, some cases might have been missed. Serological detection has better detection sensitivity.

Paediatric oncology facility at this center is facing resource constrains in form of high nurse to patient ratio, congested wards and lack of proper training of nurses and residents in paediatric oncology. However, improvement guided steps has been initiated. Arrangements have been made for isolated ward and non rotational nursing staffs. Supportive care has been improving due to:

1. Regular nurses training for complications, febrile neutropenia, cannulation, line handling and oral and anal care has been started. Twining with other tertiary cancer centre has been done to enhance their skills.
2. Concept of standing orders and procurement of medicines in anticipation has been implemented to delay the time gap of fever and antibiotics.

3. Step up facilities- General ward has segregated beds for neutropenic cases. There are two step-up units available, one a high dependency unit and other as intensive care unit.

Facility of graded step up has helped in escalation of supportive care. Impact of dose reduction and deferred schedule of induction is not known. Studies about asparaginase activity in plasma have noted better result with steady level of L-Asparaginase [23,24]. It seems reasonable to consider that deviations will cause sub-optimal leukaemia clearance, extent not known as of now. However, balancing the mortality due to sepsis or other life threatening condition, available support system and chemotherapy schedule will remain individual consultant decision and study is needed to document all deviations and effects. Induction response in term of bone marrow remission was not associated with treatment deviations. But, it is noteworthy that all cases received minimum 2 doses of anthracyclins, 3 doses of vincristine and 6 doses of L-asparaginase along with steroid. How much reduction will actually cause induction failure is hard to conclude based on small number of cases. This study noted a high induction failure rate as compared to published Indian literature [20]. Reason might be related to inclusion of eight relapse cases, out of which three failed to achieve complete remission. Absence of cytogenetics and molecular tests is a hindrance to explore the reason of induction failure further.

Hyperglycaemia and other non sepsis side effects of induction chemotherapy have been noted rarely [25,26]. Hyperglycaemia is attributed to high dose of steroid as well as L-Asparaginase. Insulin therapy should be used to keep blood sugar in check. This study also noted four cases with hyperglycaemia, steroid induced, occurred during first week of steroid. As first week of therapy was not having L-Asparaginase, steroid was considered as causation. Two cases developed seizure during induction and both were having no CNS disease at onset. Causation of seizure in CNS disease free induction cases are variable and it might be due to posterior reversible encephalopathy syndrome, thrombosis, and bleeding or methotrexate toxicity by intrathecal methotrexate administration [27-29]. The concentration of intrathecal methotrexate was 5 mg/mL which was higher than recommended concentration by paediatric ALL protocols. L-Asparaginase related CNS events were less likely as MRI were normal in all cases. Transient methotrexate toxicity was considered and next dose on-ward; methotrexate was administered in more dilution (in 10 mL sterile water).

Limitation(s)

Study has limitations of inadequate baseline information regarding biochemical, and molecular parameters. Karyotyping was not done on any of patient and mutation data were also very limited. Logistic limitations were the cause. Effect of poor risk features like complex karyotype, hypoploidy, Philadelphia or MLL positivity on induction response and tolerance is not known. Sepsis workup was more focused on bacterial culture and no viral culture was attempted even in cases with no growth in bacterial culture. Baseline nutritional assessment was limited to height and weight and no details of other nutritional marker were present in evaluated files. It could have bearing on tolerance of therapy.

CONCLUSION(S)

This study depicts feasibility of administrating high intensity induction chemotherapy in ALL cases even in limited infrastructure setting. Despite logistic limitations and lack of isolation for all cases, a good result and acceptance of induction is feasible in paediatric oncology unit at peripheral area.

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